REMARKS

The final Office Action mailed September 8, 2009, has been received and carefully considered. The Examiner's allowance of claim 24 is again acknowledged with thanks.

Claims 16-27 are pending in the Application and are submitted to be in allowable condition. Claims 16, 24, and 25 are independent.

The continued rejection of claims 16-13 and 25-27 under 35 U.S.C. §103(a) as unpatentably obvious over Baltzer et al. or English et al., these in view of Xiong et al. (2004), is respectfully traversed for the reasons given in the following.

Summary –

(1) The disclosures of Baltzer et al. and English et al. do not mention mutual prodrugs that include Applicants' specific type of β-lactam antibiotic, cephalosporins and specific type of β-lactamase inhibitors, sulbactams. The Examiner acknowledges that, "neither [sic Baltzer et al. and English et al.] used the exact permutation of β-lactam antibiotic and β-lactamase inhibitor."

(2) Contrary to the Examiner's assertion that Baltzer et al. forms a mutual prodrug "in the exact same way applicants do" and that English et al. links sulbactam "in the same way" to a penicillin, Applicants respectfully disagree. Applicant' starting materials (cephalosporin s and sulbactams, see formulas II and III on page 1 of Applicants' specification) and reaction sequences (Methods 1 and 2, see pages 6 and 7 of the Third Substitute Specification) are different so that different pathways, not mere esterification, are needed to prepare Applicants' cephalosporin ester compound and salts thereof.

(3) While the disclosure of Xiong et al. (2004) addresses the problem of β-lactam antibiotic resistance of three class A β-lactamases encoded by a single plasmid of *Klebsiella pneumonia,* and tests various β-lactam antibiotics including sulbactams and cephalosporins, the disclosure of Xiong et al. (2004) does not relate to mutual prodrugs and therefore does not supply the disclosure missing in Baltzer et al. and English et al. needed for a *prima facie* case of obviousness.

(4) Selection of a particular species from among a very large class of β-lactam antibiotics having a broad range of properties is not *prima facie* obvious. The β-lactamase resistant cephalosporin ester compound and salts thereof according to the present invention have indisputable novelty which differs, as being more precisely presented, from the combined disclosures of Baltzer et al. or English et al. taken with Xiong (2004).

(5) Applicants respectfully disagree that one of ordinary skill in this art would extrapolate from the mutual prodrug examples presented by Baltzer et al. and English et al. and assume that all β-lactam antibiotics, such as Applicants' cephalosporin, in combination with all β-lactamase inhibitors, such as Applicants' sulbactams (a) could be combined in a single molecule, (b) would function as a mutual prodrug, and (c) would have advantages over a simple combination.

(6) The matrix of possible compounds of this mutual prodrug genus is simple too large to reasonably encompass Applicants' mutual prodrug species, cephalosporins in combination with sulbactams, as obvious. Mere general comments about possible applicability of the prodrug concept in the Title of Baltzer et al. and the Examiner's linking of sulbactam of English et al. with penicillin and mention of 'Similar application to other drugs' do not rise to making

obvious Applicants' compound and Applicants' discovery of its properties. To say this would have a chilling effect on advancements in this art and would be contrary to the overriding constitutional standard of support for advancements to be implemented by the Commissioner and the courts.

(7) Applicants believe that the age of the Baltzer et al. article (1980) and the English et al. article (1989) support Applicants' position of novelty and non-obviousness of Applicants' specific type of mutual prodrug as claimed which Applicants consider solves a long felt but previously unsolved need in additiona to providing a mutualprodrug with improved aqntibacterial effect as presented in Applicants' experimental results in Applicants' specification.

(8) In view of the foregoing points regarding independent claims 16, 24, and 25, and the claims depending there from for analogous reasons, Applicants respectfully submit that no *prima facie* case of obviousness has been made out by the combined disclosures of Baltzer et al. or English et al. in view of Xiong et al. (2004) so that these grounds of rejection should be withdrawn.

Discussion –

Baltzer et al. v. Xiong et al. (2004)

1. The Baltzer et al. article is titled "Mutual pro-drugs of β-lactam antibiotics and β-lactamase inhibitors" and was received for publication in July, 1980. The introductory summary describes,"[T]he "principle of combining a β-lactam antibiotic with a β-lactamase inhibitor in a single molecule functioning as pro-drug for the two active components is illustrated...ampicillin and mecillinam, respectively, are combined with penicillanic acid sulfone and produced esters which were excellently absorbed from the gastro-intestinal tract and after absorption hydrolyzed

with simultaneous liberation of the active components. ... The advantages of "mutual pro-drugs" over simple combinations are discussed."

2. The Examiner considers that Baltzer et al. establishes that "one of ordinary skill in the art would be well motivated to prepare the mutual prodrug rather than the combination of β-lactam antibiotic and β-lactamase inhibitor, because the advantage to doing that is taught" (see the last sentence in the paragraph bridging pages 2 and 3 of the Action).

3. Contrary to the Examiner's position, Applicants respectfully disagree that an artisan would extrapolate from the two penicillin-type prodrug examples presented by Baltzer et al. and assume that all β-lactam antibiotics and all β-lactamase inhibitors (a) could be combined in a single molecule, (b) would function as a pro-drug, and (c) would have advantages over a simple combination. The matrix of possible compounds of this genus is simple too large to reasonably encompass Applicants' mutual prodrug species, cephalosporins in combination with sulbactams, as obvious. The disclosure of Baltzer et al. does not mention Applicants' mutual prodrug species, cephalosporins in combination with sulbactams and, since the disclosure of Xiong et al. (2004) does not relate to a mutual prodrug but merely lists test results for various β-lactam antibiotics, Xiong et al. (2002) is not considered to supply the missing disclosure. T he disclosure of Xiong et al. (2004) addresses the problem of β-lactam antibiotic resistance of three class A β-lactamases encoded by a single plasmid of *Klebsiella pneumonia,* and tests various β-lactam antibiotics including sulbactams and cephalosporins, the disclosure of Xiong et al. (2004) does not relate to prodrugs and therefore does not supply the missing disclosure needed for a *prima facie* case of obviousness.

English et al. v. Xiong et al. (2004)

4. The English et al. article is titled "Orally Effective Acid Prodrugs of the β-lactamase inhibitor Sulbactam" and was received for publication in March, 1989. The introductory summary describes,"Sulbactam (1) is a β-lactamase inhibitor with limited oral bioavailability. Lipophilic double-ester prodrug sulbactam pivoxil (2) significantly improves the oral absorption of sulbactam, as does the mutual prodrug double ester sultamicillin (3)....Carboxyl-terminated double esters have several potential advantages over their nonionizable lipophilic counterparts, including water solubility, crystallinity, choice of salts for dosage forms, and formation of innocuous byproducts on hydrolysis."

5. The Examiner considers that, "English has a very similar teaching [sic to Baltzer et al.]. Again, sulbactam is linked in the same way to a penicillin. ..... The 'Similar application to other drugs' would render such an approach obvious to any other drug which was already known to be synergistic with sulbactam."

6. The Examiner further contends, in the first full paragraph on page 3 of the Action, that, "The two examples of the primary reference, compounds 3 and 4, both employ sulbactam as the β-lactamase inhibitor. The β-lactam antibiotic in both cases is a penicillin. However, it would be obvious to use any "β-lactam antibiotic", as that is what the reference Baltzer teaches; again, see title and above cited paragraph. Likewise, English teaches 'other drugs' ".

7. At the top of page 5 of the Action the Examiner states, "The only reason that these references don't anticipate is that neither used the exact permutation of β-lactam antibiotic and β-lactamase inhibitor." The Examiner combines the disclosures of Baltzer et al. and Xiong et al. (2004), and the disclosures of English et al. and Xiong et al. (2004). The Examiner contends on page 4 of the Action, "In Xiong (2004), note Table 2, which shows strong synergism between

sulbatam and Cephalothin, Cefuroxime, Cefpodoxime, Cefotaxime, Ceftazidime and Ceftriaxone. Note that cefuroxime is the second species in claim 16."

8. The disclosure of English et al. does not mention Applicants' mutual prodrug species, cephalosporins in combination with sulbactams and, since the disclosure of Xiong et al. (2004) does not relate to a mutual prodrug but merely lists test results for various β-lactam antibiotics, Xiong et al. (2004) is not considered to supply the missing disclosure. The disclosure of Xiong et al. (2004) addresses the problem of β-lactam antibiotic resistance of three class A β-lactamases encoded by a single plasmid of *Klebsiella pneumonia,* and tests various β-lactam antibiotics including sulbactams and cephalosporins, the disclosure of Xiong et al. (2004) does not relate to prodrugs and therefore does not supply the missing disclosure needed for a *prima facie* case of obviousness.

9. Thus, contrary to the Examiner's position, Applicants respectfully disagree that an artisan would extrapolate from the pro-drug examples presented by English et al. and assume that all β-lactam antibiotics and all β-lactamase inhibitors (a) could be combined in a single molecule, (b) would function as a pro-drug, and (c) would have advantages over a simple combination. The matrix of possible mutual prodrug compounds of this genus is simple too large to reasonably encompass a mutual prodrug including Applicants' mutual prodrug species, cephalosporins in combination with sulbactams, as obvious. The disclosure of English et al. does not mention Applicants' specific type of β-lactam antibiotics, cephalosporins, and, while the disclosure of Xiong et al. (2004) does not supply the missing disclosure needed for a *prima facie* case of obviousness as discussed in paragraph (8) above.

General Arguments

10. All and all, therefore, it appears to Applicants that the Examiner has taken the view that because penicillins, a type of β-lactam antibiotic, and sulbactams, a type of β-lactamase inhibitor, have been mentioned in the prior art, *ergo* all mutual prodrugs – known and unknown - such as Applicants' novel mutual prodrug species, cephalosporins in combination with sulbactams, are obvious ... because the Examiner considers that one of ordinary skill in the art would be motivated to achieve them by the teaching of the prior art.

11. Applicant respectfully believes that the Examiner's position is based on mistaken concepts that would have a chilling effect on advancements in the art the support of which is the overriding constitutional standard to be implemented by the Commissioner and the courts.

12. First, the class of β-lactam antibiotics is broad and includes, for example, penicillin derivatives, cephalosporins, monobactams, carbopenems and β-lactamase inhibitors, i.e., any antibiotic agent that contains a β-lactam nucleus in its molecular structure". Moreover, β-lactam antibiotics is the most widely-used class of antibiotics.

13. Applicants do not believe that an artisan would find it obvious to combine a specific kind of β-lactam antibiotic from among the most widely-used class of antibiotics with any β-lactamase inhibitor simply because of the broad prodrug Title of the Baltzer et al. article and/or the broad comment, "Similar application to other drugs", in the English et al. article. The artisan would wonder if specific kinds of β-lactam antibiotics and specific kinds of β-lactamase inhibitors (a) could be combined in a single molecule, (b) would function as a pro-drug, and (c) would have advantages over a simple combination. Additionally, contrary to the Examiner's positions, Applicants do not believe that an artisan would have any expectation of an advantage from such a vast matrix of possible combinations. The matrix of possible compounds of this

mutual prodrug genus is simple too large to reasonably encompass Applicants' mutual prodrug species, cephalosporins in combination with sulbactams, as obvious.

14. In particular, Applicants believe that it is not well founded for the Examiner to have concluded merely from the comment in Engliah et al. that "Similar application to other drugs", "would render such an approach obvious to any other drug which was already known to be synergistic with sulbactam". Mere general comments about possible applicability of the prodrug concept in the Title of Baltzer et al. and the Examiner's linking of sulbactam of English et al. with penicillin and mention of 'Similar application to other drugs' do not rise to making obvious Applicants' compound and Applicants' discovery of its properties. To say this would have a chilling effect on advancements in this art and would be contrary to the overriding constitutional standard of support for advancements to be implemented by the Commissioner and the courts.

15. Penicillins and cephalosporins have a core structure that is a Beta-lactam ring or penam, which is possessed by all β-lactam antibiotics, even through each of them has its own unique complete structure. The disclosures of Baltzer et al. and English et al., and Xiong et al. (2004) do not teach or suggest a mutual prodrug of Applicants' specific type. In particular, there is no disclosure or suggestion of preparation of a series of Applicants' β-lactamase resistant cephalosporin ester compounds and salts thereof, as well as their use for preparation of antibiotic compositions and the specific advantages obtained for this species of mutual prodrugs that include Applicants' specific type of β-lactam antibiotic, cephalosporins and specific type of β-lactamase inhibitors, sulbactams from among the very large genus of β-lactam antibiotics.

16. When read as a whole as prior art references must be read, it is clear that the disclosures of Baltzer et al., English et al., and Xiong et al. (2004) do not teach or suggest Applicants' specific type of β-lactam antibiotic, cephalosporin. Thus, Applicants submit that the present invention would not be arrived at even by motivated artisans. Merely indication of a concept with a Title or an implication that a mutual prodrug is expected to be prepared, as Baltzer et al. did, and mere wording like "Similar application to other drugs", as English et al. stated are, in fact, mere general comments about possible applicability of the prodrug concept . These general comments, Applicants submit, do not rise to making obvious Applicants' compound and Applicants' discovery of its properties.

17. Indeed, Applicants believe that the age of the Baltzer et al. article (1980) and the English et al. article (1989) support Applicants' position of non-obviousness of Applicants' specific type of β-lactam antibiotic – Cephalosporin - of Applicants' β-lactamase resistant cephalosporin ester compound and salts thereof. Applicants have provided a novel pro-drug and thus have solved a long felt but previously unsolved need. In part, this was made possible by Applicants' novel intermediate compound according to allowable claim 24 used in Applicants' Method 2 which includes a protective group to synthesize YR 3-6 (see the Third Substitute Specification, page 7, lines 26-31).

18. Applicants believe that the selection of a mutual prodrug species including a β-lactam antibiotic from among a large class of β-lactam antibiotics is not *prima facie* obvious. Applicants submit that the β-lactamase resistant cephalosporin ester compound and salts thereof according to the present invention have indisputable novelty which differs, as being

more precisely presented, from the combined disclosuresof Baltzer et al. or English et al. taken with Xiong (2004).

19. Applicant's β-lactamase resistant cephalosporin ester compound is characterized in that the structures of the compound are composed by connecting methyl ester residue of sulbactam halomethyl ester with carboxyl residue of semi-synthetic cephalosporin or salts thereof is employed together with what the inorganic salt can be as, as recited in Applicant's Specification pages 2-3, and supported by the whole content of the Application. To this extent the problem of the present invention could be seen as the preparation of another compound or pharmaceutical salts thereof characterized in that the compound is represented by formula (I), see claims 16 and 25.

20. From the point of view of the problem addressed by the present invention, Applicants' have prepared a mutual prodrug that is a β-lactamase resistant cephalosporin ester compound and salts thereof that have *improved* antibacterial effect, e.g., as presented in the Experimental results on page 21 and pages 23-24 respectively. In contrast, the combined disclosures of Baltzer et al. or English et al. taken with Xiong et al. (2004) do not give any indication for selection of the more precisely prescribed β-lactamase resistant cephalosporin ester compound and salts thereof according to the independent claims 16 and 25, and the claims depending therefrom, from among the enormous number of possible β-lactamase inhibitors and β-lactam antibiotics for an alleged mutual prodrugs, in either Baltzer et al. or English et al. taken with Xiong et al. (2004).

21. Thus, Applicants respectfully submit that the Examiner's contention of obviousness is mistaken, not well founded, and should be withdrawn. Applicants believe that the concept of

a prodrug without selection of the more precisely prescribed substances cannot take away the novelty and does not render obviousness Applicants' claims.

22. With regards to the Examiner's position on page 4 of the Action, the first full paragraph, that, "In Xiong (2004), note Table 2, which shows strong synergism between sulbactam and Cephalothin, Cefuroxime, Cefpodoxime, Cefotaxime, Ceftazidime and Ceftriaxone. Note that cefuroxime is the second species in claim 16.", Applicants respectfully submit that the Examiner has made a conclusion based on a wrong concept. Table 2 merely show "Results of susceptibility testing for transformants", which, as stated by Xiong et al. (2004) on page 266, under "4. Discussion", merely indicates "...the **possibility** of horizontal transfer of the resistance gene." Please note that therein is no indication in Xiong et al. (2004) for selection of the more precisely prescribed β-lactamase resistance, nor any improved antibacterial effect having been given unlike provided by Applicants' Experiment results on page 21 and pages 23-24 of the present Application.

23. Applicants independent claim 16 (a β-lactamase resistant cephalosporin ester compound and salts thereof) and independent claim 25 (pharmaceutical salt of a β-lactamase resistant cephalosporin ester compound) are compound claims and are supported by Applicants' disclosure of methods for making the compounds recited (see Applicants' Method 1 and Method 2 on pages 6 and 7 of Applicants' specufucation). Contrary to the Examiner's assertion that Baltzer et al. forms a mutual prodrug "in the exact same way applicants do" and that English et al. links sulbactam "in the same way" to a penicillin, Applicants respectfully disagree. Applicant' starting materials (cephalosporin s and sulbactams, see formulas II and III on page 1 of Applicants' specification) and reaction sequences (Methods 1 and 2, see pages 6

and 7 of the Third Substitute Specification) are different so that different pathways, not mere esterification, are needed to prepare Applicants' cephalosporin ester compound and salts thereof. Thus Applicants respectfully disagree. The methods disclosed in Baltzer et al. and English et al. are not the same, and do not even pertain to the precisely prescribed substances as recited in Applicants' independent claims 16 and 25. Indeed, Applicants believe that, given the problem to be solved, neither the methods of the prior art individually, nor their respective combination with the generally available knowledge of one of ordinary skill in this art, would make the solution according to the present invention with the advantageous effects achieved obvious.

24. In view of the foregoing points regarding independent claims 16, 24, and 25, and the claims depending there from for analogous reasons, Applicants respectfully submit that no *prima facie* case of obviousness has been made out by the combined disclosures of Baltzer et al. or English et al. in view of Xiong et al. (2004) so that these grounds of rejection should be withdrawn.

CONCLUSION

In view of the foregoing remarks and arguments, Applicants submit that claims 16-27 and the Application are in condition for allowance. Reconsideration and passage of this case to issue are therefore requested.

Should the Examiner consider that a conference would help to expedite the prosecution of this Application, the Examiner is invited to contact the undersigned to arrange for such an interview.

Request For Extension of Time

Applicants request a first extension of time for responding to the Office Action dated September 8, 2009. A first extension fee of $65.00 is submitted herewith by credit card payment. Should the remittance be accidentally missing or insufficient, the Commissioner is hereby authorized to charge the fee to our Deposit Account No. 18-0002 and is requested to advise us accordingly.

Respectfully submitted,

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Date

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